REMARKS

This amendment is being filed in response to Office Action mailed September 30, 2002. Claims 1 to 61 are pending. Claims 1 to 38, 41 to 44 and 57 to 61 stand withdrawn from consideration as directed to a non-elected invention. By the present amendment, claim 40 has been canceled without prejudice. Applicants maintain the right to prosecute the cancelled claim in any related application claiming the benefit of priority of the subject application. New claims 62 to 72, which depend from elected claim 39, or substantially parallel elected but now canceled claim 40, have been added. Accordingly, upon entry of the amendment, claims 39,45 to 56 and 62 to 72 are under consideration.

Regarding the Amendments

The amendments to the specification were made to address typographical errors. The amendments to claims 39, 47, 52 and 55 are supported by the specification or were made to address various informalities. In particular, the amendment to claim 39 to recite soluble "MAFA extracellular domain that inhibits" binding of the NK- or the T cell-expressed cell surface MAFA to its target cell ligand is supported, for example, at page 2, lines 13-16; page 2, line 29, to page 3, line 3; and page 26, lines 24-26. The amendment to claim 47, which depends from claim 39, to recite soluble "MAFA extracellular domain" was made in view of the amendment to claim 39 reciting "MAFA extracellular domain." The amendment to claim 52 to delete the recitation of "preventing or inhibiting the NK- or T cell- expressed cell surface MAFA from" was made in order to delete redundant language already recited in claim 51, for which claim 52 depends. The amendment to claim 55 to recite "secretion of a" cytokine was made to more clearly indicate that one or more cytokines may be secreted. Thus, as the amendments to the specification and claims are supported by the specification or were made to address various informalities, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 62 to 72 are supported by the specification. In particular, claims 62 to 64, which ultimately depend from claim 39, are supported, for example, at page 18, line 22, to page 20, line 21. Claims 65 to 72 substantially parallel claims 39, 40 and 45 to 56, as originally filed and, therefore, are supported by originally filed claims 39, 40 and 45 to 56. Support for the

recitation of "agonist anti-MAFA antibody or a subsequence of an agonist anti-MAFA antibody" can be found, for example, in originally filed claim 40 and at page 10, lines 13-17, and lines 20-21. Thus, as new claims 62 to 72 are supported by the specification no new matter has been added and entry thereof is respectfully requested.

I. OBJECTIONS TO THE DISCLOSURE AND DRAWINGS

The disclosure stands objected to due to various informalities. As set forth above, Applicants have amended the specification in order to correct the informalities. As to the ATCC no., Applicants respectfully request that this objection be held in abeyance until notification of allowable subject matter. Accordingly, Applicants respectfully request withdrawal of the objection to the specification.

The drawings stand not approved. Submitted herewith are corrected drawings prepared in accordance with the PTO 948 Drawing Review. Accordingly, Applicants respectfully request acceptance of the drawings.

II. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 39, 40 and 45 to 56 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. The grounds for rejection appear to be based upon the alleged absence of guidance for "any soluble agent," for "any subsequence of any anti-MAFA antibody," for "preventing or stimulating NK or T cell cytolytic activity....in vivo."

The specification enables claims 39, 40 and 45 to 56, as originally filed. Nevertheless, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, the claims have been amended and claim 40 has been canceled herein without prejudice thereby rendering the rejection moot as to this claim. The rejection will therefore be addressed as it may pertain to the amended claims and new claims.

Amended claims 39 and 45 to 56 and new claims 62 to 64 recite "soluble MAFA extracellular domain." The specification teaches how to make and use soluble MAFA extracellular domain without undue experimentation.

As to making soluble MAFA, the specification discloses three mammalian MAFA sequences, human, rat and mouse (see, e.g., page 18, line 24 to page 20, line 21). The specification exemplifies a particular soluble MAFA extracellular domain sequence, mouse

MAFA amino acids 64 to 188 (see, e.g., page 26, lines 24-26), which is capable of stimulating NK cell cytotoxic activity (page 10, line 22; page 25, line 26; page 30, lines 27-29; see, also, Figure 3). The specification also teaches how to make MAFA polypeptides and nucleic acids encoding MAFA polypeptides (page 17, line 25, to page 18, line 21; page 20, lines 32 to page 21, line 7; and page 26, line 24 to page 27, line 29). Furthermore, in addition to the various mammalian MAFA sequences known in the art, the various functional regions of MAFA, including the ITIM motif, transmembrane region, and glycosylation sites are known in the art (see, e.g., the Blaser *et al.* and Hanke *et al.* references, Figures 1 and 2, respectively, cited in the Office Action).

The specification also discloses routine assays for identifying soluble MAFA extracellular domain having the requisite activity. For example, the specification discloses that MAFA equivalents can be identified by "routine screening for their ability to specifically bind to a MAFA target cell or target cell ligand" or "routine screening for their ability as soluble polypeptide to block the interaction of an NK cell or T cell surface MAFA to interact with an MAFA target cell or a MAFA target cell ligand" (page 13, lines 3-10). The specification exemplifies NK cell cytotoxicity and CTL activity assays, for example, at page 28, lines 12-19, such assays further known in the art at the time of the invention (Sentman *et al.*, *Nat. Immun. Cell Growth Regul.* 7:95 (1988); and Franco, *J. Immunol.* 162:3388 (1999)).

Thus, in view of the fact that the specification teaches the structure and function of soluble MAFA extracellular domain, exemplifies soluble MAFA extracellular domain having the requisite activity and how to make and identify soluble MAFA extracellular domain, one skilled in the art could make soluble MAFA extracellular domain having the requisite activity without undue experimentation.

New claims 65 to 72 recite "agonist anti-MAFA antibody or subsequence of the agonist anti-MAFA antibody." The specification teaches how to make and use agonist anti-MAFA antibody and subsequences of the agonist anti-MAFA antibody without undue experimentation.

As to making agonist anti-MAFA antibody, the specification discloses how to produce polyclonal and monoclonal anti-MAFA antibodies using a variety of methods (page 22, line 16 to page 23, line 12). The specification exemplifies producing anti-MAFA antibodies, which resulted in the isolation of two antibodies, 1F10 and 7B5 (page 28, line 21 to page 29, line 19),

having the requisite agonist activity (page 29, line 20, to page 30, line 7; see, also, page 31, lines 4-18). Such methods are applicable generally in producing additional agonist anti-MAFA antibody.

As to making subsequences and other forms of agonist anti-MAFA antibody, the specification discloses various methods including, for example, chemical and recombinant synthesis, chimeric and humanization using recombinant and *in vivo* methods, as well as using phage display methods (see, for example, page 11, line 13 to page12, line 15). The Patent Office will appreciate that methods of producing antibodies and antibody fragments binding to antigen, mimetics, modified forms, and variants thereof (e.g., amino acid substitutions, additions and deletions) are all routine in the art, as evidenced by the numerous references cited in the specification (see also, page 13, lines 11 to page 15, line 11).

In regard to the cited Kuby *et al.*, Ngo *et al.* and Abaza *et al.* references, these references were published in 1992 and in 1994, and cannot fairly be said to represent the start of the art at the time the application was filed in 2001. Furthermore, even if for the sake of argument some experimentation is needed in order to practice the full scope of the claimed invention, simply because experimentation may be needed does not render the claims inadequately enabled. The proper legal standard is whether the experimentation is "undue." In re Angstadt, 537 F.2d 498, 504 (CCPA 1976); In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)

Here, the level of skill in the art is high. For example, numerous routine methods for producing proteins including antibodies having amino acid substitutions, deletions and additions, as well as mimetics thereof, are disclosed in the specification and such routine methods are known in the art (see, e.g., page 26, line 11 to page 15, line 15; page 20, line 37, to page 23, line 12; and the references cited in the specification). Furthermore, screening proteins for the requisite activity is also routine in view of the guidance in the specification and other assays known the art (see, e.g., page 28, lines 12-19, and the Sentman and Franco references cited therein and discussed above). Thus, given the guidance in the specification and knowledge in the art for producing proteins including antibodies having amino acid substitutions, deletions and additions, as well as mimetics thereof, undue experimentation would not be needed.

The present case is analogous to In re Wands where the Federal Circuit held that even though experiments were needed to identify which hybridomas produced the desired antibodies, in view of the guidance in the specification and knowledge in the art which was high, undue

experimentation would not be required to practice the invention. Id. As such, it cannot fairly be said that it would require undue experimentation to produce and screen for soluble MAFA extracellular domain, agonist anti-MAFA antibody or subsequences thereof having substitution, deletion or addition. Accordingly, this grounds for rejection should properly be withdrawn

Thus, in view of the fact that the specification teaches how to make agonist anti-MAFA antibodies and subsequences of agonist anti-MAFA antibodies, exemplifies two particular antibodies having the requisite agonist activity, one skilled in the art could make agonist anti-MAFA antibody and subsequences of agonist anti-MAFA antibody without undue experimentation.

As to using soluble MAFA, and agonist anti-MAFA antibodies and subsequences of agonist anti-MAFA antibodies, the specification discloses in vitro, *ex vivo* and *in vivo* uses (page 6, lines 12-13). As to *in vivo* uses in particular, Applicants note that the proper standard for enablement is whether one skilled in the art would accept that the model is reasonably correlating to the condition. In re Branna, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

Here, the claims are directed to inhibiting an NK- or a T cell expressed cell surface MAFA binding to a ligand on a target cell by providing a soluble MAFA extracellular domain, agonist anti-MAFA antibody or subsequence of an agonist anti-MAFA antibody that inhibits the binding of the NK- or the T cell-expressed cell surface MAFA to its target cell ligand; and contacting the soluble MAFA extracellular domain, agonist anti-MAFA antibody or subsequence of the agonist anti-MAFA antibody to the NK or the T cell or the target cell in an amount sufficient to inhibit cell surface MAFA binding to the ligand on the target cell. The cytotoxic activity assays disclosed in the specification that demonstrate in vitro activity of soluble MAFA extracellular domain and agonist anti-MAFA antibody are predictive of what one skilled in the art would expect *in vivo*. First, MAFA, also referred to as KLRG1, is a naturally occurring molecule expressed on NK cells and virally activated T cells that inhibits cytokine production and NK cell-mediated cytotoxicity (see, for example, the specification page 2, lines 3-5, page 9, lines 5-9; and page 10, lines 13-15 and lines 20-30; see also, Corral *et al.*, *Eur. J. Immunol.* 30:920 (2000); McMahon *et al.*, *J. Immunol.* 169:1444 (2002); and Beyersdorf *et al.*, *Eur. J. Immunol.*31:3443 (2001)). Second, those skilled in the art have long recognized that NK and T-cells participate in immune responsiveness including killing virally infected cells and tumor

cells. (Herberman, RB, *Semin. Oncol.* 29:27 (2002); Miller, JS, *Cancer Invest.* 20:405 (2002); and Brutkiewicz *et al., Crit. Rev. Oncol. Hematol.* 41:287 (2002)). Thus, given that 1) MAFA is an endogenous molecule expressed on NK cells and T-cells which modulates cytotoxicity and cytokine secretion; and 2) that NK cells and T-cells mediate immune response and participate in killing virally infected cells and anti-tumor responses *in vivo*, the in vitro data disclosed in the specification demonstrating that soluble MAFA extracellular domain and agonist anti-MAFA antibody increase and decrease NK cytotoxicity, respectively, are evidence sufficient to predict *in vivo* activity of soluble MAFA extracellular domain and agonist anti-MAFA antibody. Given that the skilled artisan would predict *in vivo* activity based upon the in vitro data disclosed in the specification, the in vitro model "reasonably correlates" with the *in vivo* condition. As such, one skilled in the art could use soluble MAFA extracellular domain, agonist anti-MAFA antibody and subsequences of agonist anti-MAFA antibody without undue experimentation as claimed.

In sum, in view of the guidance in the specification regarding MAFA structure and function, the three mammalian MAFA sequences and the exemplified soluble MAFA and the two agonist anti-MAFA antibodies, and the methods for producing and identifying additional soluble MAFA and agonist anti-MAFA antibodies and subsequences thereof having the requisite activity, and further in view of the role of MAFA in modulating NK and T cell functions and that NK and T cells participate in immune responses including killing virally infected cells and tumor cells, one skilled in the art could practice claims 39, 45 to 56 and 62 to 72 without undue experimentation. As such, claims 39, 45 to 56 and 62 to 72 are adequately enabled by the specification. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement be withdrawn.

The rejection of claims 39, 40 and 45 to 56 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. The grounds for rejection appear to be based upon the alleged lack of written description for "any soluble agent," and for "any subsequence of any anti-MAFA antibody."

An adequate written description for claims 39, 40 and 45 to 56, as originally filed is provided. Nevertheless, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, the claims have been amended and claim 40 has been canceled herein without prejudice thereby rendering the rejection moot as to this claim.

The rejection will therefore be addressed as it may pertain to the amended claims and new claims.

As set forth above, the specification teaches the structure and function of soluble MAFA extracellular domain and exemplifies soluble MAFA extracellular domain having the requisite activity. The specification further discloses three mammalian MAFA sequences, human, rat and mouse, such sequences known in the art at the time of the invention (page 18, line 24 to page 20, line 21). The specification exemplifies a soluble MAFA extracellular domain sequence, mouse MAFA amino acids 64 to 188 capable of stimulating NK cell cytotoxic activity (page 26, lines 24-26; page 10, line 22; page 25, line 26; page 30, lines 27-29; see, also, Figure 3). In addition, as set forth above, various MAFA functional regions, including the ITIM motif, transmembrane region, and glycosylation sites are known in the art (see, e.g., the cited Blaser *et al.* and Hanke *et al.* references, Figures 1 and 2, respectively). Thus, in view of the teachings in the specification and knowledge in the art, one skilled in the art would be apprised of a genus of soluble MAFA extracellular domain. As such, an adequate written description for soluble MAFA extracellular domain is provided.

As to subsequences of anti-MAFA antibody, as set forth above the specification teaches how to make antibodies having the requisite activity and exemplifies two antibodies, 1F10 and 7B5, having that activity. The specification further teaches anti-MAFA antibody subsequences. For example, the specification discloses antigen binding portions such as Fab, VL, VH, CL and CH1 domains; Fv; dAb and isolated CDR, to name a few (page 11, line 19, to page 12, line 15). Given the fact that such antibody fragments and many others are well known in the art and that methods of producing such antibody fragments and many others are also well known in the art, as evidenced by the numerous references cited in the specification, those skilled in the art would be apprised of the anti-MAFA antibody subsequences recited in the claimed methods. As such, an adequate written description for anti-MAFA antibody subsequences is provided.

In sum, in view of the fact that those skilled in the art would recognize soluble MAFA extracellular domain, anti-MAFA antibodies and subsequences of anti-MAFA antibodies, claims 39, 45 to 56 and 62 to 72 are adequately described. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 40, 52, 55 and 56 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is respectfully traversed. The grounds for rejection are based upon several claims terms.

Claims 40, 52, 55 and 56 are clear and definite as written. As set forth above, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, the claim 55 has been amended to recite "a cytokine," and claim 40 has been canceled herein without prejudice thereby rendering the rejection moot.

As to the recitation of "stimulates" in claim 52, as disclosed in the specification MAFA (e.g., soluble MAFA) decreases or inhibits the ability of cell surface MAFA to interact with ligand expressed on a target cell. (page 9, lines 5-9). Thus, by preventing or inhibiting NK- or T cell expressed cell surface MAFA from generating an inhibitory signal to the NK or the T cell this stimulates an activity of the NK or the T cell. Thus, in view of the specification claim 52 is clear and definite as written.

As to the recitation of cytokine in claim 55, amended claim 52 recites "a cytokine" indicating that one or more cytokines can be secreted. In this regard, the Examiner correctly points out that multiple cytokines can be secreted by a single cell and those skilled in the art understand that multiple cytokines may be secreted by a T cell. The Examiner will also agree that those skilled in the art know what a cytokine is. Thus, in view of the fact that those skilled in the art know what a cytokine is and also know that multiple cytokines can be secreted by a T cell, the meaning of "cytokine" is clear and definite to those skilled in the art. As such, amended claim 55 is clear and definite.

In view of the amendments and foregoing remarks, claims 52, 55 and 56 are clear and definite. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. §102 and 103(a)

The rejection of claims 39, 40 and 46 to 56 under 35 U.S.C. §102(b) as allegedly anticipated by WO 98/54209 is respectfully traversed. The grounds for rejection appear to be based upon WO 98/54209 describing "preventing T cell activation in human (mammal) which

could lead to the prevention of tumor growth by administering a pharmaceutical composition comprising soluble agent such as antibody to human MAFA or fragment thereof."

Claims 39, 40 and 46 to 56, as originally filed, are not anticipated by WO 98/54209. Nevertheless, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, the claims have been amended and claim 40 has been canceled herein without prejudice thereby rendering the rejection moot as to this claims. The rejection will therefore be addressed as it may pertain to the amended claims and new claims.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir. 1990).

As disclosed in the specification, activating NK and T cell activity is useful for killing tumor cells (see, e.g., page 10, lines 28-30). The Examiner acknowledges that WO 98/54209 describes "a method for preventing T cell activation." [see page 9, para. 13 of the Office Action] Thus, WO 98/54209 does not describe claims 39 and 46 to 56, directed to soluble MAFA extracellular domain that inhibits the binding of the NK- or the T cell-expressed cell surface MAFA to its target cell ligand to inhibit cell surface MAFA binding to the ligand on the target cell, which in turn can stimulate T cell activation. As to claims 62 to 72, WO 98/54209 does not teach or suggest, *inter alia*, an agonist anti-MAFA antibody or a subsequence of an agonist anti-MAFA.

In view of the fact that WO 98/54209 does not describe claims 39 and 46 to 56, nor claims 62 to 72, WO 98/54209 can not anticipate these claims. Accordingly, as WO 98/54209 does not anticipate claims 39, 46 to 56 and 62 to 72, the rejection under 35 U.S.C. §102(b) should properly be withdrawn.

The rejection of claim 45 under 35 U.S.C. §103(a) as allegedly unpatentable over WO 98/54209 is respectfully traversed. The grounds for rejection appear to be based upon WO 98/54209 describing *in vivo* contacting and that in vitro contacting is an obvious variation.

As discussed above, the Examiner acknowledges that WO 98/54209 describes "a method for preventing T cell activation;" however claim 45, which depends from claim 39, is directed to soluble MAFA extracellular domain that inhibits the binding of the NK- or the T cell-expressed

cell surface MAFA to its target cell ligand to inhibit cell surface MAFA binding to the ligand on the target cell, which in turn can stimulate T cell activation. Thus, as WO 98/54209 teaches preventing T cell activation, it cannot fairly be said that WO 98/54209 teaches or suggests stimulating T cell activation. Furthermore, *inter alia*, WO 98/54209 fails to teach or suggest soluble MAFA extracellular domain. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

As to new claims 62 to 72, WO 98/54209, *inter alia*, fails to teach or suggest soluble MAFA extracellular domain. Accordingly, claims 62 to 72 would not have been obvious at the time of the invention in view of WO 98/54209.

The rejection of claims 39, 51 to 53, 55 and 56 under 35 U.S.C. §103(a) as allegedly unpatentable over WO 98/54209 in view of Blaser *et al.* (*J. Immunol.* 161:6451 (1998)) and Hanke *et al.* (Eur. *J. Immunol.* 28:4409 (1998)) is respectfully traversed. The grounds for rejection appear to be based upon Blaser *et al.* purportedly describing MAFA as "an inhibitory receptor on NK cells and viral infected (activated) CD8 T cytotoxic cells" and that purportedly "activated T cell (viral infection) increases MAFA expression and T cell-mediated killing." Hanke *et al.* purportedly describe "2F1 antigen, which is a mouse homolog of rat MAFA receptor that binds to MAFA on NK cells and may modulate immunological response" and that purportedly "MAFA expression is associated with increase NK cell killing."

Claims 39, 51 to 53, 55 and 56, as originally filed, would not have been obvious at the time of the invention in view of WO 98/54209, Blaser *et al.* or Hanke *et al.* alone, or in any combination. Nevertheless, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, the claims have been amended and claim 40 has been canceled herein without prejudice thereby rendering the rejection moot as to this claim. The rejection will therefore be addressed as it may pertain to the amended claims and new claims.

In order for a rejection to be proper under 35 U.S.C. §103, *inter alia*, there must have been a motivation to modify or combine the references at the time of the invention; the combination of references must teach or suggest each and every element of the claimed invention; and there must have been a reasonable expectation of success at the time of the invention. Here, *inter alia*, the cited references, even if combined, fail to teach or suggest each

and every element of the claimed invention, nor was there a reasonable expectation of success at the time of the invention.

In particular, for example, neither WO 98/54209, Blaser *et al.* nor Hanke *et al.* teach or suggest a soluble MAFA extracellular domain or an agonist anti-MAFA antibody or a subsequence of an agonist anti-MAFA antibody. Absent such a teaching or suggestion, claims 39, 45 to 56 and 62 to 72 would not have been obvious in view of WO 98/54209, Blaser *et al.* or Hanke *et al.* alone, or in any combination.

Furthermore, as discussed above the Examiner has acknowledged that WO 98/54209 describes "a method for preventing T cell activation....by administering....human MAFA or fragment thereof." Since the methods of claims 39, 45 to 56 and 62 to 64, can result in stimulating T cell activation, WO 98/54209 teaches the skilled artisan away from producing claims 39, 45 to 56 and 62 to 64.

In sum, in view of the fact that neither WO 98/54209, Blaser *et al.* nor Hanke *et al.* teach or suggest a soluble MAFA extracellular domain or an agonist anti-MAFA antibody or a subsequence of an agonist anti-MAFA antibody and that WO 98/54209 teaches the skilled artisan away from producing claims 39, 45 to 56 and 62 to 64, claims 39, 45 to 56 and 62 to 72 would not have been obvious at the time of the invention. Accordingly, the rejection under 35 U.S.C. §103(a) should properly be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 39, 45 to 56 and 62 to 72 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

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